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IMPACT OF INSULIN RESISTANCE AND PHYSICAL ACTIVITY ON KIDNEY STONE FORMATION IN THE JAPANESE POPULATION: A PROSPECTIVE COHORT STUDY

Ryosuke Ando,[1] Sadao Suzuki,[2] Takeshi Nishiyama[2], Hiroko Nakagawa[2], Akihiro Hosono[2], Miki Watanabe[2], Tamaki Yamada[3], Kazumi Taguchi[1], Shuzo Hamamoto[1], Atsushi Okada[1], Keiichi Tozawa[1], Kenjiro Kohri[1], Takahiro Yasui[1]

[1] Department of Nephro-urology & [2] Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. [3] Okazaki City Medical Association, Public Health Center, Aichi, Japan.

Abstract

INTRODUCTION AND OBJECTIVE: Development of kidney stones has been linked to metabolic syndrome, which is characterized by insulin resistance (IR). In this prospective study, we followed the baseline cohort for 5 years. This study aimed to examine the impact of IR and physical activity on incident kidney stones.

METHODS: A prospective cohort study was performed involving 4,007 (2,084 men and 1,923 women) participants aged 35–79 years who voluntarily underwent medical examinations between April 2007 and August 2011 and were found free of kidney stones. Follow-up data were obtained at 5 years after baseline examination. Participants with diabetes mellitus or fasting glucose level ≥140 mg/dL at baseline were excluded. Based on homeostasis model assessment of insulin resistance (HOMA-IR) and fasting insulin levels, the participants were divided into three groups: 1) "Control" group: HOMA-IR <2.5 and insulin <15.0 μU/mL; 2) "Moderate IR" group: HOMA-IR ≥2.5 and insulin <15.0 μU/mL; and 3) "Severe IR" group: HOMA-IR ≥2.5 and insulin ≥15.0 μU/mL. None of the participants had low HOMA-IR and high insulin level. Demographic variables and physical activities including walk and sedentary times were compared among the three groups. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for incident kidney stones at 5 years after baseline.

RESULTS: A total of 97 men (4.7%) and 45 women (2.3%) developed kidney stones at 5 years after baseline. At baseline, 1,878 men and 1,812 women were classified into the Control group, 158 men and 91 women into the Moderate IR group, and 48 men and 20 women into the Severe IR group. Body mass index, abdominal circumference, blood pressure, and triglycerides were significantly higher and high-density lipoprotein cholesterol was significantly lower, in the order corresponding to the Control, Moderate IR, and Severe IR groups. After adjustment for multiple variables, the Severe IR group was associated with kidney stone formation (OR, 2.91; 95% CI, 1.02–8.25) in men. Meanwhile, there was no difference between IR and kidney stone formation in women. Sedentary lifestyle was associated with IR.

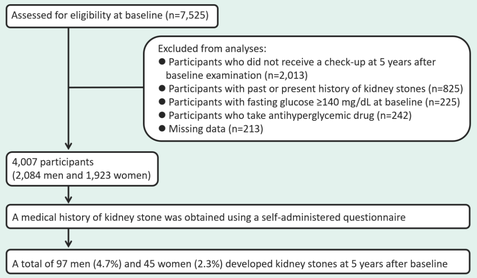
CONCLUSIONS: In Japanese men, severe IR was associated with kidney stone formation under normoglycemic conditions. Avoiding sedentary lifestyles could prevent kidney stone formation through improving IR.

Background & objective

- Kidney stone development has been linked to metabolic syndrome, which is characterized by insulin resistance (IR) and hyperinsulinemia.
- Effects of insulin resistance/hyperinsulinemia under the normoglycemic condition on kidney stone formation has been unclear.
- The aim of this study was to examine the impact of IR on incident kidney stones.

Study design & participants

- A prospective cohort study was performed in 7,525 (4,161 men and 3,364 women) participants aged 35–79 years who voluntarily underwent medical examinations between April 2007 and August 2011.
- Follow-up data were obtained at 5 years after baseline examination.



Definition of insulin resistance (IR)

n=4,007		Fasting insulin level (μU/mL)	
		< 15.0	≥ 15.0
HOMA-IR	< 2.5	Control n=3,690 (1,878 men, 1,812 women)	none
	≥ 2.5	Moderate-IR n=249 (158 men, 91 women)	Severe-IR n=68 (48 men, 20 women)

- HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405
- There were no participants who had low HOMA-IR under high insulin level.

Statistical analysis

- The demographic variables were calculated and tabulated according to the 3 groups (control, moderate-, and severe-IR, respectively).
- Logistic regression analysis was used to estimate the OR and 95% CI for kidney stone development within each of the 3 groups.
- All data were analyzed according to sex.
- All the statistical analyses were performed for crude and multivariate-adjusted models using the Statistical Analysis System, version 9.4 (SAS Institute, Cary, NC) , and significance was defined as $P < 0.05$.

Results

Table 1. Demographics of control, moderate and severe insulin resistance (IR) groups

Men (n=2,084)	Control	Moderate-IR	Severe-IR	p for trend
No. pts	1,878	158	48	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (yr)	59.0 ± 10.5	57.6 ± 11.1	55.8 ± 11.3	0.01
BMI (kg/m^2)	23.0 ± 2.5	26.1 ± 2.8	28.2 ± 3.5	< .0001
Waist circumference (cm)	82.8 ± 7.2	90.7 ± 7.2	96.7 ± 8.8	< .0001
Systolic BP (mm Hg)	127.3 ± 16.1	134.5 ± 15.4	138.6 ± 15.8	< .0001
Fasting glucose (mg/dL)†	98.0 ± 9.8	107.3 ± 10.8	105.8 ± 12.4	< .0001
Triglyceride (mg/dL)†	115.3 ± 69.3	160.4 ± 103.7	180.3 ± 140.6	< .0001
Cholesterol (mg/dL)†				
Total	204.2 ± 31.3	207.3 ± 31.9	207.2 ± 34.9	0.27
HDL	64.0 ± 16.4	52.8 ± 11.5	52.9 ± 14.5	< .0001
Fasting insulin (μU/mL)	4.8 ± 2.1	11.6 ± 1.8	19.3 ± 4.9	< .0001
HOMA-IR	1.2 ± 0.5	3.1 ± 0.4	5.1 ± 1.5	< .0001

Women (n=1,923)	Control	Moderate-IR	Severe-IR	p for trend
No. pts	1,812	91	20	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (yr)	55.4 ± 9.9	58.6 ± 9.6	56.3 ± 9.0	0.003
BMI (kg/m^2)	21.8 ± 2.8	24.7 ± 3.1	29.3 ± 3.3	< .0001
Waist circumference (cm)	79.4 ± 8.2	88.0 ± 7.4	95.5 ± 7.8	< .0001
Systolic BP (mm Hg)	121.0 ± 16.5	135.4 ± 19.1	135.7 ± 14.9	< .0001
Fasting glucose (mg/dL)†	92.8 ± 8.4	104.4 ± 11.3	107.7 ± 10.7	< .0001
Triglyceride (mg/dL)†	85.4 ± 43.3	126.0 ± 51.0	136.8 ± 46.1	< .0001
Cholesterol (mg/dL)†				
Total	212.7 ± 33.7	222.9 ± 35.8	202.9 ± 24.6	0.10
HDL	76.3 ± 17.3	63.8 ± 14.3	56.9 ± 9.0	< .0001
Fasting insulin (μU/mL)	4.9 ± 2.0	11.6 ± 1.6	19.6 ± 4.4	< .0001
HOMA-IR	1.1 ± 0.5	3.0 ± 0.4	5.2 ± 1.4	< .0001

† Conversion factor was mg/dL to mmol/L × 0.05551 for glucose, × 0.01129 for tryglyceride and × 0.02586 for cholesterol.

Table 2. Crude and multivariate adjusted odds ratio (OR) for kidney stone development within control, moderate and severe insulin resistance (IR) groups

Men (n=2,084)	Control	Moderate-IR	Severe-IR	p for trend
No. pts	1,878	158	48	
Kidney stone development, n (%)	87 (4.6)	5 (3.2)	5 (10.4)	
OR (95% CI)				
Crude	1.00	0.67 (0.27-1.68)	2.39 (0.29-1.96)	0.40
Multivariate adjusted†	1.00	0.76 (0.29-1.96)	**2.91 (1.02-8.25)**	0.24

Women (n=1,923)	Control	Moderate-IR	Severe-IR	p for trend
No. pts	1,812	91	20	
Kidney stone development, n (%)	43 (2.4)	2 (2.2)	0 (0.0)	
OR (95% CI)				
Crude	1.00	0.92 (0.22-3.88)	NA	0.58
Multivariate adjusted†	1.00	1.31 (0.30-5.79)	NA	0.95

† Adjusted for age, BMI, waist circumference and systolic blood pressure.

Table 3. Physical activity (walking and sedentary times)

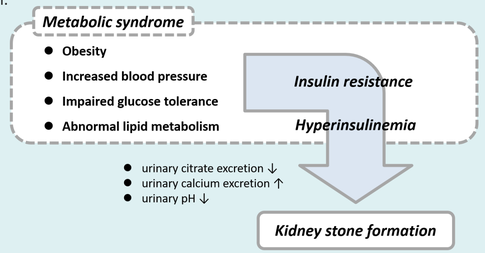
Men (n=2,084)	Control	Moderate-IR	Severe-IR	p value †
No. pts	1,878	158	48	
Walking time (hours/day)				0.01
2 or greater	636 (33.9)	37 (23.4)	13 (27.1)	
1 or less	1,242 (66.1)	121 (76.6)	35 (72.9)	
Sedentary time (hours/day)				< .0001
6 or less	1,105 (58.8)	81 (51.3)	15 (31.3)	
7 or greater	773 (41.2)	77 (48.7)	33 (68.7)	

Women (n=1,923)	Control	Moderate-IR	Severe-IR	p value †
No. pts	1,812	91	20	
Walking time (hours/day)				0.09
2 or greater	847 (46.7)	42 (46.2)	4 (20.0)	
1 or less	965 (53.3)	49 (53.8)	16 (80.0)	
Sedentary time (hours/day)				0.31
6 or less	1,265 (69.8)	57 (62.6)	14 (70.0)	
7 or greater	547 (30.2)	34 (37.4)	6 (30.0)	

† Mantel-Haenszel chi-square test.

Discussions

- Even in the normoglycemic condition, age, BMI, systolic BP, and triglycerides were significantly higher and HDL-cholesterol was significantly lower in the moderate- and severe-IR groups than control group; furthermore, significant positive trends were observed in both sexes.
- High insulin resistance and hyperinsulinemia could contribute to the development of calcium stones by lowering urinary citrate excretion, or increasing urinary calcium excretion.



Conclusions

- In Japanese men, hyperinsulinemia (≥15.0 μU/mL) was associated with kidney stone formation under the normoglycemic condition.
- Avoiding sedentary lifestyles could prevent kidney stone formation through improving insulin resistance.